array set having a recognition moiety bound to at least one of the electrodes or to a non-conducting substance disposed between the electrodes.

39. (Twice Amended) A method according to Claim 24, wherein said device is an electronic device for determining one or more targets in a sample, comprising:

an integrated circuit comprising the first group of N_1 conductors and a second group of N_2 conductors, defining between them N_1xN_2 junctions, each such junction being formed with an electronic module comprising two electrodes, each one linked to or defined as an integral portion of one of the conductors, and comprises a diode or non-linear component permitting current flow through the electronic module only in the direction from the first group of conductors to the second group of conductors, whereby a current flowing between one conductor of the first group to one conductor of the second group of conductors defines a single junction point between them; each pair of electrodes forming part of an array set, each array set having a recognition moiety bound to at least one of the electrodes or to a non-conducting substance disposed between the electrodes.

REMARKS

Claims 1-42 are pending herein. By this Amendment, claims 2, 3, 27, 28, 32 and 33 are amended to delete allegedly unconventional and improper claim language objected to by the Patent Office. Claim 11 is amended to correct an alleged spelling error and to ensure proper antecedent basis for the term "monomers." Claims 1, 10, 24-26, 34, 35 and 37-19 are also amended to revise allegedly confusing language. The specification is amended to revise the references to drawings under the heading Brief Description of the Drawings.

The attached Appendix includes a marked-up copy of each rewritten paragraph (37 C.F.R. §1.121(b)(1)(iii)) and claim (37 C.F.R. §1.121(c)(1)(ii)).

No new matter is added.

I. Title

The Patent Office alleged that the title of the invention is not descriptive, and that a new title is required that is clearly indicative of the invention to which the claims are directed.

The title has been amended to recite "Detection of a Biological Moiety in a Sample." Applicants submit that the amended title clearly and concisely describes the present invention.

Reconsideration and withdrawal of the objection are respectfully requested.

II. Drawings

The Patent Office alleged that Figure 30 does not contain part 901 as referenced in the specification on page 57, line 12.

Accompanying this Amendment is a Request for Approval of Drawing Correction in which Fig. 30 is proposed to be revised to show part 901 which was unintentionally mislabeled "900" due to a typographical error. In the originally filed Fig. 30, both electrodes were labeled as 900, when one of the electrodes was meant to be labeled as 900, and the other labeled as 901.

Reconsideration and withdrawal of the objection and approval of revised Fig. 30 are respectfully requested.

III. Specification

Under the Brief Description of Drawings heading, the Patent Office alleged that Figure 1 is referenced to, but there are Figures 1A and 1B in the drawings. The Patent Office alleged that appropriate correction is required here, and similarly in Figures 2, 5-7, 9, 10, 12, 13, 21 and 25.

By this Amendment, the paragraphs referencing Figs. 1, 2, 5-7, 9, 10, 12, 13, 21 and 25 listed under the Brief Description of Drawings heading are amended to reference Figures 1A and 1B, 2A-2D, etc., as suggested by the Patent Office.

Reconsideration and withdrawal of the objection are respectfully requested.

IV. Claim Objections

Claims 2, 3, 27, 28, 32 and 33 were objected to by the Patent Office for allegedly using terminology deemed unconventional and improper. The objection is respectfully traversed.

By this Amendment, claims 2, 3, 27, 28, 32 and 33 are amended to delete allegedly unconventional and improper terminology. In particular, these claims have been amended to delete terminology such as, for example, (c1), (c2), (a0), etc. Applicants submit that the objection to the claims is overcome and respectfully request reconsideration and withdrawal of the objection.

Claim 17 was objected to by the Patent Office for allegedly using the phrase "any one of the preceding." The objection is respectfully traversed.

Claim 17 was previously amended by Preliminary Amendment (filed October 26, 2000) to amend the phrase "any one of the preceding claims" to "Claim 1." Thus, Applicants submit that no further amendment to claim 17 is required. Reconsideration and withdrawal of the objection are respectfully requested.

Claim 11 was objected to by the Patent Office for allegedly misspelling the term "polyanyline." The objection is respectfully traversed.

By this Amendment, claim 11 is amended to revise "polyanyline" to read "polyaniline." Reconsideration and withdrawal of the objection are respectfully requested.

V. Claim Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-34, 36 and 42 were rejected by the Patent Office under 35 U.S.C. §112, second paragraph for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The rejection is respectfully traversed.

In particular, the Patent Office rejected claims 1-34, 36 and 42 for allegedly using the confusing phrase "either to one or more of at least two electrodes and/or on the substrate."

By this Amendment, the phrase "either to one or more of at least two electrodes and/or on the substrate" has been amended to recite "to one or more of the at least two electrodes, onto a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate ...". This is found in the original specification, for example, at page 7, lines 27-29. Applicants submit that this language is not confusing and places the claims in a condition for allowance. Reconsideration and withdrawal of the rejection are respectfully requested.

The Patent Office also rejected claim 11 as allegedly lacking antecedent basis for the term "monomers."

Claim 11 is revised by this Amendment to reference claim 10 instead of claim 6. Claim 10 refers to "monomers" in line 12. Applicants submit antecedent basis now exists for the monomers of claim 11. Reconsideration and withdrawal of the rejection are respectfully requested.

VI. Claim Rejections Under 35 U.S.C. §102(b)

Claims 1-9, 17-25, 30 and 42 were rejected by the Patent Office under 35 U.S.C. §102(b) as allegedly being anticipated by Mroczkowski et al. (U.S. Patent No. 5,284,748). The rejection is respectfully traversed.

The present invention claims a system for assaying one or more targets in a sample comprising an assay device, an electric or electronic module and reagents. The assay device has one or more assay sets for at least each target to be assayed. Each assay set comprises at least two electrodes and a recognition moiety immobilized to one or more of the at least two electrodes, onto a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate. The recognition moiety is capable of specific binding to one of the targets. The module determines the electric conductance between the at least two electrodes of each assay set. The reagents are used for growing a conducting substance from nucleation center-forming entities deposited onto or bound to a complex formed between the recognition moiety and the target. A substance then forms a conductive bridge between at least two of the electrodes of a set. (See claim 1).

Mroczkowski describes a method for detecting the occurrence of a binding or complex-forming reaction between specific substances by utilizing the binding reaction to modify an electrical circuit. The substance to be detected is one of a pair of first and second substances that undergo a specific binding reaction with each other. Mroczkowski makes use of different method steps and system components than the present invention, and therefore fails to disclose each and every aspect of the present invention.

Mroczkowski includes the steps of mixing the sample with particles under conditions effective to cause binding of the first substance, if present in the sample, to the surface of the particles. The particles having the first substance bound to the surfaces thereof are contacted with a layer of the second of the two substances. This layer forms a path between a pair of spaced-apart electrical conductors superposed on a substantially non-electrically conductive base. The layer of the second substance is bound to the base such that the bind reaction between the first and second substances causes the particles to be bound to the path in aggregates.

Mroczkowski further includes the steps of removing the particles that are bound to the path as a result of non-specific binding and particles that are not bound to the path. The exposed outer surfaces of the aggregates are then coated with an electrically conductive substance that adheres selectively to the particles forming the aggregates but which does not adhere to the remainder of the path. The electrically conductive substances which remain un-adhered to the aggregates are removed, and each of the conductors are connected to an electrical circuit that includes a source of electrical energy. Finally, the change in the electrical current flow through the circuit caused by formation of the coated aggregates on the path and the electrical change indicating the level of the substance to be detected in the test sample is measured.

The present invention is novel over Mroczkowski in three primary aspects.

First, Mroczkowski discloses that a layer of the second of said pair of substances, i.e., the moiety that binds to the substance to be detected (essentially corresponding to the recognition moiety of the present application) must form a path between the pair of spaced-apart electrical conductors. This means that the Mroczkowski detection method requires that the gap between the two spaced apart electrodes has to be a priori essentially spanned by a layer of the second of the pair of substances (i.e., recognition moieties).

The present invention does not require or claim that the recognition moiety span the gap between the two electrodes. In fact, according to claim 1 of the present invention, the recognition moiety may be immobilized on one or both of the electrodes or on the substrate between the two electrodes. The present invention does not require the recognition moiety to form a continuous path or to connect the electrodes as disclosed in Mroczkowski.

Second, Mroczkowski discloses that the first and second substances bound together must form aggregates, i.e., an association of a plurality of particles together, in order to provide a conductive bridge between the two spaced apart electrodes.

The present invention does not require an association of a plurality of complexes between the recognition moiety and the targets in order to form a bridge between the two electrodes. In other words, the present invention does not require formation of aggregates as described in Mroczkowski. In the present invention, there are a plurality of complexes between the recognition moiety and the targets. Only a single complex between a recognition moiety and a target is sufficient, after the growth of the conductive material, to form a conductive bridge between the two electrodes.

Third, Mroczkowski coats the aggregates with an electrically conductive substance, i.e., the core of an essentially non-conductive aggregate is coated with an outer layer of a conductive material.

The present invention does not coat aggregates with an electrically conductive substance as the present invention does not claim the formation of aggregates. Thus there is no need in the present invention to coat aggregates.

In the present invention, there is no need for a continuous path or recognition moieties, and no need for formation of aggregates. This stems from the fact that the conductive bridge between the two spaced apart electrodes in the present invention are not formed merely by coating existing aggregates as in Mroczkowski. The present invention instead has a conductive bridge that forms between two spaced apart electrodes by growth in a crystalline-like formatting procedure of conductive substances from nucleation-center forming entities, which is not taught or suggested by Mroczkowski.

This crystalline-like formation of a conductive layer from nucleation-center forming entities renders the system of the invention so sensitive that even a single complex between a single target and a single recognition moiety (creating a single nucleation-center forming entity) is sufficient to produce electric coupling between two electrodes due to the development of the conductive layer.

The claimed system and method is uniquely sensitive over disclosures such as Mroczkowski. This is evident in the specification, for example, at page 11, lines 23-29, wherein it is stated:

> The nucleation-center forming entities may serve as a nucleus for growth of a conductive substance, which eventually connects between the two electrodes thereby forming a conductive bridge between the electrodes. Thus, the system of the present invention, is highly sensitive allowing the formation of a conductive bridge even where few, or even a single complex between a recognition moiety and a target is formed between or in the electrodes of an assay set.

The fact that the present invention enables growth of a conductive substance, even from a single nucleation-center forming entity, indicates that the present invention is far more sensitive than the situation concerning merely the coating of relatively large aggregates as disclosed in Mroczkowski.

Thus, Applicants submit that Mroczkowski fails to disclose a system and method for assaying one or more targets in a sample comprising reagents for growing a conducting substance from nucleation center-forming entities deposited onto or bound to a complex formed between a recognition moiety and a target, wherein the conducting substance forms a conductive bridge between at least two electrodes of an assay set.

For the foregoing reasons, Applicants submit that Mroczkowski fails to anticipate the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

VII. Claim Rejections Under 35 U.S.C. §103(a)

A. Claims 12-16 and 29

Claims 12-16 and 29 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Mroczkowski in view of JP 04-148669 (JP '669). The rejection is respectfully traversed.

Claim 12 recites that the one or more targets of claim 1 are one or more nucleic acid sequences. Claim 14 recites that the recognition moiety of claim 1 is immobilized on at least one electrode of each assay.

As extensively set forth above, Mroczkowski fails to teach or suggest the present invention. In particular, Mroczkowski fails to teach or suggest a system and method for assaying one or more targets in a sample comprising reagents for growing a conducting substance from nucleation center-forming entities deposited onto or bound to a complex formed between a recognition moiety and a target, wherein the conducting substance forms a conductive bridge between at least two electrodes of an assay set as claimed in claim 1.

Mroczkowski requires the formation of a layer of the second pair of substances, i.e., the target, which will form a path between the spaced-apart electrical conductors. The outer surface of this layer is comprised of "target" aggregates that are coated with an electrical conducting substance to confer the system with its conductance. The Mroczkowski method does not work in samples with a low target concentration, but must contain a minimum amount of target sufficient to achieve the necessary continuous layer.

The present invention enables the formation of a conductive bridge between two electrodes even in samples with low target concentrations. This is because formation of the conductive bridge depends solely on the formation of at least a complex between the recognition moiety and the target that forms the nucleation center on which the conductive bridge grows. There is no need for the formation of a layer of the target spanning between the two electrodes as taught in Mroczkowski.

Further, the Patent Office admits that Mroczkowski fails to teach or suggest DNA as in the present invention.

JP '669 fails to remedy the deficiencies of Mroczkowski. JP '669 teaches a method for extending and securing macromolecules such as DNA by using two aluminum electrodes installed on a substrate.

The present invention claims the formation of nucleation centers, and does not require the extension of DNA or any other target or recognition moiety which may form part of the recognition pair between the two electrodes. As long as there is at least one recognition moiety immobilized either to one or more of the at least two electrodes and/or to the substance between them to which the target may be bound, a conducting bridge will grow between the two electrodes.

The mere fact that JP '669 teaches the use of DNA does not render the claimed invention obvious because, like Mroczkowski, JP '669 fails to teach or suggest a system and method for assaying one or more targets in a sample comprising reagents for growing a conducting substance from nucleation center-forming entities deposited onto or bound to a complex formed between a recognition moiety and a target, wherein the conducting substance forms a conductive bridge between at least two electrodes of an assay set as claimed in claim 1.

Further, nothing in JP '669 would have motivated one of ordinary skill in the art to combine the teachings of JP '669 with Mroczkowski to develop the present invention.

For the foregoing reasons, Applicants submit that Mroczkowski and JP '669, whether taken singly or in combination, fail to teach or suggest the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claims 31-33

Claims 31-33 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Mroczkowski. The rejection is respectfully traversed.

Claim 31 claims a kit for use in assaying one or more targets in a sample comprising an assay device and reagents for growing a conducting substance from nucleation center-forming entities deposited onto or bound to a complex formed between the recognition moiety and the target. The conducting substance forms a conductive bridge between at least two of the electrodes of a set. The assay device comprises one or more assay sets, wherein there is at least one assay set for each target to be assayed. Each assay set comprises at least two electrodes and a recognition moiety immobilized either to one or more of the at least two electrodes and/or onto a substrate between the at least two electrodes. The recognition moiety is capable of specific binding to one of the targets.

Mroczkowski fails to teach or suggest the present invention. Mroczkowski has been extensively discussed above showing how the reference fails to teach or suggest the present system and method for assaying a target. Likewise, Mroczkowski fails to teach or suggest the kit of claims 31-33.

In particular, Mroczkowski fails to teach or suggest a kit for assaying a sample comprising at least two electrodes and a recognition moiety immobilized either to one or more of the at least two electrodes and/or onto a substrate between the at least two electrodes. Mroczkowski also fails to teach a recognition moiety capable of specific binding to one of the targets.

By admission of the Patent Office, Mroczkowski fails to teach or suggest a kit. From the teachings of Mroczkowski, one may be able to design a kit in which a conducting substance is used to coat an outer surface of a layer of target molecules, but the teachings and suggestions of Mroczkowski would not have led one to make use of reagents according to the present invention to form a conducting bridge by growing a conducting substance from nucleation centers.

For the foregoing reasons, Applicants submit that Mroczkowski fails to teach or suggest the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

C. Claims 34-41

Claims 34-41 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Mroczkowski in view of Hisada et al. (U.S. Patent No. 5,914,505). The rejection is respectfully traversed.

Claim 34 claims a kit for use in assaying one or more targets in a sample comprising an assay device and reagents. The reagents comprise monomers of a conducting polymer which can bind to the target or tow a complex formed between the recognition moiety and the target in such a way that upon polymerization of the monomers, a conducting bridge between the at least two electrodes of a set is formed. The assay device comprises one or more assay sets, wherein there is at least one assay set for each target to be assayed. Each assay set comprises at least two electrodes and a recognition moiety immobilized either to one or more of the at least two electrodes and/or onto a substrate between the at least two electrodes. The recognition moiety is capable of specific binding to one of the targets. Claims 35-37 relate to the multiplexing assay configuration. Claim 37, as opposed to claims 35 and 36, claims an assay device with a vertical configuration.

As set forth above, Mroczkowski fails to teach or suggest a kit for for assaying a sample comprising at least two electrodes and a recognition moiety immobilized either to one or more of the at least two electrodes and/or onto a substrate between the at least two electrodes. Mroczkowski also fails to teach that the recognition moiety is capable of specific binding to one of the targets.

By admission of the Patent Office, Mroczkowski fails to teach or suggest a kit and/or junction forming diodes (claim 35). From the teachings of Mroczkowski, one may be able to

design a kit in which a conducting substance is used to coat an outer surface of a layer of target molecules, but the teachings and suggestions of Mroczkowski would not have led one to make use of reagents according to the present invention to form a conducting bridge comprising polymerized monomers of a conducting polymer bound to the target or to the complex formed between the recognition moiety and target.

Hisada fails to remedy the deficiencies of Mroczkowski. Hisada teaches a semiconductor integrated circuit. Hisada was made to solve the problem of large output noises, achieved by the formation of a multibit structure. (See column 1, lines 26-36). Even if Hisada describes the multiplexed system as alleged by the Patent Office, the construction described by Hiasada is for the purpose of preventing the malfunction of an internal circuit due to output noises and not for the simultaneous detection of several targets.

The present invention does not claim multiplexed systems, but does claim the construction of assay arrays in such a way so as to detect a number of targets simultaneously. Hisada would not have been relied upon by one of ordinary skill in the art because it is not analogous art.

Thus, Applicants submit that one would not have been motivated to have combined the teachings of Mroczkowski and Hisada to produce the present invention.

For the foregoing reasons, Applicants submit that Mroczkowski and Hisada, whether taken singly or in combination, fail to teach or suggest the present invention.

D. Claims 10, 11, 26-28 and 34

Claims 10, 11, 26-28 and 34 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over Mroczkowski in view of Yang et al. (U.S. Patent No. 5,563,424). The rejection is respectfully traversed.

The present invention claims a method for assaying one or more targets in a sample comprising an assay device, an electric or electronic module for determining electric

conductance between the at least two electrodes of each assay set, and reagents comprising monomers of a conducting polymer that can bind to a complex formed between the recognition moiety and the target in such a way that upon polymerization of the monomers, a conducting bridge between the at least two electrodes of each set is formed.

As set forth extensively above, Mroczkowski fails to teach or suggest the present invention wherein In particular, Mroczkowski fails to teach or suggest a system for assaying one or more targets in a sample comprising at least two or more electrodes and a recognition moiety immobilized to one or more of the at least two electrodes and/or substrate between the two electrodes, wherein the recognition moiety is capable of specific binding to one of the targets.

Yang fails to remedy the deficiencies of Mroczkowski. Yang describes polymer grids comprising a body of an electrically conducting organic polymer such as polyaniline. According to Yang, the polymer grid is prepared, i.e., polymerized, and then incorporated onto the electronic device to form a homogeneous coating of the device. This homogeneous film may be in the form of a thin film.

The present invention, however, makes use of the monomers of polyaniline. In the present invention, it is only after binding to a complex formed between the target and the recognition moiety that the monomers start to polymerize to form the conducting bridge. Thus, unlike Yang, in the present invention, if the complex has not formed, no polymer is present.

Further, the polymer grids of Yang are known to affect electronic performance and light emission. Therefore, even if one were to hypothetically assume that the Yang polymer grids are present in the present invention (which is not the case), Yang does not teach or suggest the use of such polymer grids for the detection, either qualitative or quantitative, of a target in a sample that is complexed to an immobilized recognition moiety.

Thus, nothing taught or suggest in Yang would have motivated one to have combined the teachings of Yang with Mroczkowski to produce the present invention.

For the foregoing reasons, Applicants submit that Mroczkowski and Yang, taken either singly or in combination, fail to teach or suggest the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

VIII. Conclusion

In view of the foregoing amendments and remarks, Applicants submit that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1-42 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone number listed below.

Respectfully submitted,

James A. Oliff
Registration No. 27,075

David M. Lafkas
Registration No. P-50,424

JAO:DML/rxg

Attachment:
Appendix

Date: January 9, 2002

OLIFF & BERRIDGE, PLC
P.O. Box 19928
Alexandria, Virginia 22320
Telephone: (703) 836-6400

DEPOSIT ACCOUNT USE AUTHORIZATION
Please grant any extension necessary for entry;
Charge any fee due to our Deposit Account No. 15-0461

APPENDIX

Changes to Title:

The following is a marked-up version of the amended title:

~~DETECTION OF A TARGET IN A SAMPLE~~

DETECTION OF A BIOLOGICAL MOIETY IN A SAMPLE

Changes to Specification:

Page 21, lines 16-17:

~~**Fig. 1** is a~~ **Figs. 1A-1B** are schematic illustrations of an assay device in a manner of performing the assay in accordance with an embodiment of the invention~~;~~, before (Fig. 1A) and after (Fig. 1B) contact between the electrodes is obtained as a result of performing the assay.

Page 21, lines 18-19:

~~**Fig. 2** is a~~ **Figs. 2A-2D** are schematic illustrations of an assay device in a manner of performing the method in accordance with an embodiment of the invention~~;~~, before (Fig. 2A) and after (Figs. 2B-2D) contact between the electrodes is obtained by the binding of the target to the different recognition moieties.

Page 21, lines 20-23:

Figs. 3A-3E show a different combination of recognition moieties, immobilized on at least one electrode of an assay device for the detection of target entities, in accordance with several different embodiments of the invention~~;~~.

Page 21, lines 24-26:

Figs. 4A, ~~4B and~~ --4C are schematic illustrations of three embodiments of the invention where the recognition moiety is immobilized on a support member which is other than an electrode~~;~~.

Page 21, lines 27-29:

~~**Fig. 5** is a~~ **Figs. 5A-5C** are schematic ~~illustration~~ illustrations of an assay device and the performance of a method in accordance with an embodiment of the invention, ~~involving functionalization of the bridge~~ showing the assay set before (Fig. 5A) and after brought into contact with the target (Fig. 5B) to form a path for the formation of a functionalized bridge (Fig. 5C).

Page 22, lines 1-2:

~~**Fig. 6** is a~~ **Figs. 6A-6C** are schematic ~~illustration~~ illustrations of an embodiment of the invention where the concentration of the target can be determined~~;~~. Fig. 6A shows the assay device before contacting the recognition moieties with the target while, Figs. 6B and 6C show, respectively, the result of contact between the recognition moieties and low or high concentrations of the target.

Page 22, lines 3-4:

~~**Fig. 7** is a~~ **Figs. 7A-7C** are schematic ~~illustration~~ illustrations of another embodiment of the invention for determining concentration of the target in the sample. Fig. 7A shows the assay device before contacting the recognition moieties with the target while, Figs. 7B and 7C show, respectively, the result of contact between the recognition moieties and low or high concentrations of the target.

Page 22, lines 5-6:

Fig. 8 is a schematic illustration of a multiplexing embodiment of the invention for detection of a variety of different target entities~~;~~.

Page 22, lines 7-8:

~~**Fig. 9** is a~~ **Figs. 9A-9D** are schematic ~~illustrating~~ illustrations of ~~an embodiment of the invention where each two adjacent assay sets share an electrode;~~ different assay sets (Fig. 9A) which can bind to different epitopes (Fig. 9B-9D) to form a bridge in corresponding assay set, in accordance with one embodiment of the invention.

Page 22, lines 9-10:

~~**Fig. 10** illustrates~~ **Figs. 10A-10B** illustrate an assay device and method for the detection of a DNA sequence in a sample~~;~~ wherein the device is first brought into contact with the target to form a bridge between the electrodes (Fig. 10A), followed by functionalization of the bridge (Fig. 10B).

Page 22, lines 11-13:

Fig. 11 shows two exemplary current-voltage relationship of a functionalized bridge formed after metal deposition on a bridge-forming target as illustrated in Fig. 10~~;~~.

Page 22, lines 14-16:

~~**Fig. 12** illustrates~~ **Figs. 12A-12B** illustrate an assay device and method for the detection of a DNA sequence in a sample where ~~the~~ a bridge formed (Fig. 12A) is functionalized by deposition of poly-*p*-phenylene vinylene (PPV) (Fig. 12B)~~;~~.

Page 22, lines 17-18:

~~**Fig. 13** illustrates~~ **Figs. 13A-13B** illustrate another embodiment of ~~functionalizing a nucleic acid bridge~~ an assay device and method for the detection of a DNA sequence in a sample where a bridge formed (Fig. 13A) is functionalized (Fig. 13B)~~;~~.

Page 22, line 19:

Fig. 14 shows an embodiment of the invention for assaying of an antigen~~;~~.

Page 22, lines 20-21:

Fig. 15 illustrates an embodiment of immobilization of oligonucleotide recognition moieties onto the electrodes;

Page 22, lines 22-23:

Fig. 16 shows a scheme for synthesizing an oligonucleotide, as described in Example 1(a);

Page 22, lines 24-25:

Fig. 17 shows a fluorescently labeled λ-DNA bridge stretched between two gold electrodes (dark strips) 12 μm apart;

Page 22, lines 26-28:

Fig. 18 shows atomic force microscope (AFM) images of a DNA bridge coated by silver connecting two gold electrodes 12 μm apart 1.5 μm and field size;

Page 23, lines 1-5:

Fig. 19 is two terminal I-V curves of a DNA bridge coated by silver prepared according to Example 8. The arrows indicate the voltage scan direction. The solid-line curves are repeated scans and demonstrate the stability of the samples. Note the different asymmetry in the I-V curves corresponding to the two scanning directions;

Page 23, lines 6-11:

Fig. 20 shows the I-V curves of a different silver wire in which the silver growth was more extensive than in Fig. 19. The more extensive silver growth resulted in a smaller current plateau, on the order of 0.5V, and a lower resistance (13MΩ vs. 30 MΩ in Fig. 17). By driving large currents through the wire, the plateau has been eliminated to give an ohmic behavior (dashed line), over the whole measurement range;

Page 23, lines 12-13:

~~**Fig. 21 shows**~~ **Figs. 21A-21F** show a schematic representation of the steps of performing a detection assay for the presence of a nucleic acid sequence in a sample. In Fig. 21(A) two conducting electrodes are defined on an insulating substrate. In Fig. 21(B) a monolayer of oligonucleotides is constructed in the gap between the pair of electrodes. In Fig. 21(C) upon contact with the sample, the target oligonucleotide binds to the recognition moiety. In Fig. 21(D) the assay device bearing the DNA duplex is contacted with a solution for inducing the elongation of the DNA skeleton. In Fig. 21(E) the assay device is exposed to a solution containing gold colloids to form DNA molecules with pendant gold colloids; finally. In Fig. 21(F) the assay device is exposed to a solution to form a conductive path bridging the two electrodes.

Page 23, lines 14-15:

Fig. 22 shows a schematic representation of the steps of a method for preparation of a chip for nucleic acid attachment~~;~~.

Page 23, lines 16-18:

Fig. 23 shows a schematic representation of the steps of a method for covalent attachment of nucleic acid probes to the chip produced by the method described in Fig. 22~~;~~.

Page 23, lines 19-21:

Fig. 24 shows a schematic representation of an assay set comprising two electrodes being open ends of conductive layers which are separated from each other by the open ends of a non-conductive (insulating) layer~~;~~.

Page 23, lines 22-23:

~~**Fig. 25 shows**~~ **Figs. 25A-25B** show a schematic representation of a process for attaching a biotin group shown in Fig. 25(B) to target nucleic acids in a sample shown in Fig. 25(A)~~;~~.

Page 23, lines 24-25:

Fig. 26 shows schematically hybridization between biotin-containing nucleic acid targets in a sample and recognition moieties on a chip;

Page 23, lines 26-27:

Fig. 27 shows essentially the same as Fig. 26, wherein the recognition moieties are present on electrodes of Fig. 24;

Page 24, lines 1-3:

Fig. 28 shows schematically attachment of avidin-containing nucleation-center forming entities to biotin-containing targets which are present in a target-recognition moiety complex;

Page 24, lines 4-5:

Fig. 29 shows essentially the same as Fig. 28, wherein the complexes are present on the electrodes of Fig. 24;

Page 24, lines 6-7:

Fig. 30 shows schematically the process of deposition of gold in one assay set comprising two electrodes;

Page 24, lines 8-14:

Fig. 31 shows three AFM pictures of a chip which underwent a process of contact with sample, attachment of nucleation centers and exposure to reagents allowing formation of gold crystallization wherein: Fig. 31(A) shows a chip lacking DNA binding moieties. Fig. 31(B) shows a chip having binding moieties which are partially complementary to sequence of target in a sample. Fig. 31(C) shows a chip having recognition moieties which are fully complementary to target sequences;

Page 24, lines 15-18:

Fig. 32 shows AFM pictures of a single assay set comprising electrodes bridged by gold particles (right top) or non bridged by gold particles (left top) and corresponding current voltage curves (right bottom and left bottom, respectively)~~;~~.

Page 24, lines 19-20:

Fig. 33 shows an electronic detection device having a multiplexing array~~;~~.

Page 24, lines 21-22:

Fig. 34 shows schematically a multiplex array of an electronic detection device wherein each hybridization site comprises a plurality of detection sites~~;~~.

Page 24, lines 23-24:

Fig. 35 shows a microelectronic embodiment of multiplex DNA array of Fig. 33~~;~~.

Page 24, lines 25-26:

Fig. 36 shows a detailed view of cross section in plane A of Fig. 35~~;~~ ~~and~~

The following is a marked-up version of the amended claims:

1. (Amended) A system for assaying one or more targets in a sample, comprising:

(a) an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes, ~~and/or~~ onto a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets;

(b) an electric or electronic module for determining electric conductance between the at least two electrodes of each assay set; and

(c) reagents for growing a conducting substance from nucleation ~~centers~~ center-forming entities deposited onto or bound to a complex formed between said recognition

moiety and said target, which substance forms a conductive bridge between at least two of the electrodes of a set.

2. (Amended) A system according to Claim 1, wherein said reagents comprise:

(~~c1~~ i) a solution comprising nucleation-~~centers~~ center forming entities for binding to said target if present in the sample; and

(~~c2~~ ii) a combination of metal ions and a reducing agent to allow growth of said metal substance on said entities.

3. (Amended) A system according to Claim 1, wherein said reagents comprise:

(~~c1~~ i) one or more reagents to allow deposition and/or formation of said nucleation center-forming entities on a complex formed between said recognition moiety and said target; and

(~~c2~~ ii) a combination of metal ions and a reducing agent to allow growth of said metal substance from said entities.

5. (Twice Amended) A system according to Claim 2, wherein said nucleation-center forming entities are metal complexes, clusters or complexes and clusters.

7. (Amended) A system according to Claim 5, wherein said metal complexes ~~and/or~~ or clusters are gold complexes ~~and/or~~ or gold clusters.

9. (Amended) A system according to Claim 5, wherein said metal complexes ~~and/or~~ or clusters are platinum complexes ~~and/or~~ or platinum clusters.

10. (Amended) A system for assaying one or more targets in a sample, comprising:

(a) an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes, immobilized ~~and/or~~ on a

substrate between the at least two electrodes or immobilized to said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets;

(b) an electric or electronic module for determining electric conductance between the at least two electrodes of each assay set; and

(c) reagents comprising monomers of a conducting polymer which can bind to a complex formed between said recognition moiety and said target, such that upon polymerization of the monomers a conducting bridge between the at least two electrodes of a set is formed.

11. (Amended) A system according to Claim ~~6~~ 10, wherein said monomers are monomers of ~~polyanyline~~ polyaniline.

24. (Amended) A method for assaying one or more targets in a sample comprising:

(a) providing an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes; ~~and/or~~ on a substrate between the at least two electrodes or to said one or more if the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets;

(b) contacting said assay device with said sample under conditions permitting binding of targets to specific recognition moieties;

(c) contacting said device with a first reagent solutions to form nucleation-center forming entities on complexes formed between a target and a recognition moiety;

(d) connecting said device with a second reagent solution to grow a conducting metal substance from said nucleation center for a time sufficient to yield a conductive bridge between said at least two electrodes;

(e) connecting said at least two electrodes to an electric or electronic module to measure conductance between said at least two electrodes; and

(f) determining conductance between said at least two electrodes, conductance above a threshold conductance indicating the presence of a respective target in the sample.

25. (Amended) A method for assaying one or more targets in a sample, comprising:

(a) reacting the sample targets with a first reagent solution to bind nucleation-center forming entities to said targets;

(b) providing an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes, ~~and/or~~ on a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets;

(c) contacting said assay device with said sample under conditions permitting binding of targets to specific recognition moieties;

(d) contacting said device with a second reagent solution to grow a conducting metal substance from said nucleation center for a time sufficient to yield a conductive bridge between said at least two electrodes;

(e) connecting said at least two electrodes to an electric or electronic module to measure conductance between said at least two electrodes; and

(f) determining conductance between said at least two electrodes, conductance above a threshold conductance indicating the presence of a respective target in the sample.

26. (Amended) A method for assaying one or more targets in a sample, comprising:

(a) providing an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized either to one or more of the at least two electrodes, ~~and/or~~ on a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets;

(b) contacting said assay device with said sample under conditions permitting binding of targets to specific recognition moieties;

(c) contacting said device with a first reagent solution comprising monomers of a conductive polymer such that said monomers can bind to complexes formed between the targets and recognition moieties;

(d) treating said device such that said monomers will polymerize to form a conducting polymer, and thereby forming a conducting bridge between at least two electrodes of at least one assay set; and

(e) determining a conductance between said at least two electrodes, conductance above a threshold conductance indicating the presence of a respective target in the sample.

27. (Amended) A method according to Claim 26, comprising ~~the following step~~ ~~(a_0)~~ before step (a):

~~(a_0)~~ reacting the sample with a second reagent solution containing entities which can form nucleation centers for growing therefrom a conductive polymer from said monomers, such that said entities bind to said targets if present in the sample.

28. (Amended) A method according to Claim 26, comprising ~~the following step~~ ~~(a_0)~~ after step (a):

~~(a_0)~~ contacting said assay device with a second reagent solution containing entities which can form nucleation centers for growing therefrom a conductive polymer from said monomers, such that said entities bind to said targets if bound to said recognition moieties.

31. (Amended) A kit for use in assaying one or more targets in a sample, comprising:

(a) an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes, ~~and/or~~ onto a substrate between the at least two electrodes or to said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets; and

(b) reagents for growing a conducting substance from nucleation ~~centers~~ center-forming entities deposited onto or bound to a complex formed between said recognition moiety and said target, which substance forms a conductive bridge between at least two of the electrodes of a set.

32. (Amended) A kit according to Claim 31, where said reagents comprise:

(~~b~~1 i) a solution comprising nucleation-~~centers~~ center forming entities for binding to said target if present in the sample; and

(~~b~~2 ii) a combination of metal ions and a reducing agent to allow growth of said metal substance on said entities.

33. (Amended) A kit according to Claim 31, where said reagents comprise:

(~~b~~1 i) one or more reagents to allow deposition, ~~and/or~~ formation, or deposition and formation of said nucleation-center forming entities on a complex formed between said recognition moiety and said target; and

(~~b~~2 ii) a combination of metal ions and a reducing agent to allow growth of said metal substance from said entities.

34. (Amended) A kit for use in assaying one or more targets in the sample comprising:

(a) an assay device having one or more assay sets at least one for each target to be assayed; each of the assay sets comprising at least two electrodes and a recognition moiety immobilized ~~either~~ to one or more of the at least two electrodes, ~~and/or~~ onto a substrate between the at least two electrodes or onto said one or more of the at least two electrodes and onto said substrate; the recognition moiety being capable of specific binding to one of the targets; and

(b) reagents comprising monomers of a conducting polymer which can bind to the target or to a complex formed between said recognition moiety and said target, such that upon polymerization of the monomers a conducting bridge between the at least two electrodes of a set is formed.

35. (Amended) An electronic device for determining one or more targets in a sample, comprising:

an integrated circuit comprising the first group of N_1 conductors and a second group of N_2 conductors, defining between them N_1xN_2 junctions, each such junction being formed with an electronic module comprising two electrodes, each one linked to or defined as an integral portion of one of the conductors, and comprises a diode or non-linear component permitting current flow through the electronic module only in the direction from the first group of conductors to the second group of conductors, whereby a current flowing between one conductor of the first group to one conductor of the second group of conductors defines a single junction point between them; each pair of electrodes forming part of an assay set, each assay set having a recognition moiety for binding a target, bound ~~either~~ to at least one of the electrodes or to a non- conducting substance disposed between the electrodes, said target after binding to the recognition moiety forming a nucleation center for growing thereon a conducting substance to form conductance.

37. (Amended) An electric device for determining one or more targets in a sample, comprising

a microelectronic device having a plurality of layers, with a first group of conductors being defined as stripes in one or more first layers and a second group of conductors being defined as stripes in one or more second layers of the device with each of said second layers being separated from a first layer by a non-conducting substance, electrodes of the device being formed as open ends of the conductors by openings or cut-outs in a vertical direction through the layers;

each pair of electrodes forming part of an assay set, each assay set having a recognition moiety for binding a target bound ~~either~~ to at least one of the electrodes or to a non- conducting substance present between the electrodes, said target after binding to the recognition moiety forming a nucleation center for growing thereon a conducting substance to form conductance.

38. (Twice Amended) A system according to Claim 18, wherein the device is an electronic device for determining one or more targets in a sample, comprising:

an integrated circuit comprising the first group of N_1 conductors and a second group of N_2 conductors, defining between them $N_1 x N_2$ junctions, each such junction being formed with an electronic module comprising two electrodes, each one linked to or defined as an integral portion of one of the conductors, and comprises a diode or non-linear component permitting current flow through the electronic module only in the direction from the first group of conductors to the second group of conductors, whereby a current flowing between one conductor of the first group to one conductor of the second group of conductors defines a single junction point between them; each pair of electrodes forming part of an array set, each array set having a recognition moiety bound ~~either~~ to at least one of the electrodes or to a non-conducting substance disposed between the electrodes.

39. (Twice Amended) A method according to Claim 24, wherein said device is an electronic device for determining one or more targets in a sample, comprising:

an integrated circuit comprising the first group of N_1 conductors and a second group of N_2 conductors, defining between them N_1xN_2 junctions, each such junction being formed with an electronic module comprising two electrodes, each one linked to or defined as an integral portion of one of the conductors, and comprises a diode or non-linear component permitting current flow through the electronic module only in the direction from the first group of conductors to the second group of conductors, whereby a current flowing between one conductor of the first group to one conductor of the second group of conductors defines a single junction point between them; each pair of electrodes forming part of an array set, each array set having a recognition moiety bound ~~either~~ to at least one of the electrodes or to a non-conducting substance disposed between the electrodes.